



TRABALHO FINAL

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**Corneal properties and Glaucoma – a review of
the literature and meta-analysis**

Ricardo Gaspar

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Corneal properties and Glaucoma – a review of the literature and meta-analysis

Ricardo Gaspar

Orientado por:

Professor Doutor Luís Abegão Pinto

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RESUMO

Objetivo: A literatura publicada sugere que as propriedades biomecânicas da córnea, nomeadamente a espessura central da córnea (ECC) e a histerese corneana (HC), influenciam a medição da pressão intraocular (PIO). Este estudo teve como objetivo investigar a associação entre a ECC e a HC e o desenvolvimento de glaucoma.

Métodos: Revisão da literatura e meta-análise. Foram incluídos estudos observacionais, publicados entre 2006 e 2016, que integrassem um grupo-controlo e um grupo de pacientes com glaucoma em que estes dois grupos apresentassem, igualmente, a ECC e a HC como *outcomes*. Dezanove estudos foram considerados elegíveis e a diferença média (MD) daqueles parâmetros nos dois grupos foi utilizada para análise estatística.

Resultados: Estudaram-se um total de 1213 olhos com glaucoma e 1055 olhos saudáveis. A análise quantitativa revelou que a HC é significativamente mais baixa no grupo de doentes com glaucoma quando comparada com o grupo-controlo ($MD = -1.54 \mu m$, intervalo de confiança de 95% $[-1.68, -1.41]$, $P < 0.00001$). A ECC foi, também, significativamente mais baixa no grupo glaucoma quando comparada com os indivíduos saudáveis ($MD = -8.49 \mu m$, intervalo de confiança de 95% $[-11.36, -5.62]$, $P < 0.001$).

Conclusão: Os pacientes com glaucoma parecem possuir propriedades corneanas diferentes das que apresentam os indivíduos saudáveis. Os nossos resultados enfatizam a importância das propriedades biomecânicas da córnea na interpretação da PIO e devem contribuir para novos estudos sobre a influência da HC e da ECC no rastreio e diagnóstico do glaucoma.

Palavras-chave: Glaucoma • Espessura central da córnea • Histerese corneana • Meta-análise

O Trabalho Final exprime a opinião do autor e não da FML

ABSTRACT

Purpose: There is evidence suggesting that corneal biomechanical properties influence intraocular pressure (IOP) measurement, namely corneal central thickness (CCT) and corneal hysteresis (CH). This study aimed to investigate the association between CH and CCT with glaucoma development.

Methods: Review of the literature and meta-analysis of observational studies (2006-2016) including both adult glaucoma patients and a control group, reporting CCT and CH as outcomes. Nineteen studies were considered eligible and the mean difference (MD) between groups (patient - control) of both variables was used for statistical analyses.

Results: A total of 1213 glaucoma and 1055 healthy eyes were studied. Quantitative analysis suggested that CH was significantly lower in the glaucoma group compared to the control group (MD = -1.54 μm , 95% CI [-1.68, -1.41], $P < 0.00001$). The CCT was also significantly lower in the glaucoma group compared to healthy controls (MD = -8.49 μm , 95% CI [-11.36, -5.62], $P < 0.001$).

Conclusion: Glaucoma patients seem to have different corneal properties than healthy controls. Our results emphasize the importance of corneal biomechanical properties in IOP interpretation, and should trigger further studies on the influence of CH and CCT in glaucoma screening and diagnosis.

Key words: Glaucoma • Central Corneal Thickness • Corneal Hysteresis • Meta-analysis

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INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide [1, 2]. This disease consists in a chronic and progressive optic neuropathy [1, 3] characterised by loss of retinal ganglion cells [3], which leads to visual field deterioration [1, 3, 4]. Moreover, glaucoma is associated with vehicle accidents, restricted mobility and falls, thus, affecting quality of life [1]. An important risk factor in glaucoma is intraocular pressure (IOP), and its decrease is the mainstay of treatment [3].

Measurement of IOP has been a matter of debate for years. In 1950, Goldmann introduced a way of measuring IOP that is currently the gold standard - applanation tonometry [3–5]. However, this device is related to the elasticity of the cornea, which means that it is dependent on its thickness and hysteresis [4]. Goldmann assumed that the average central corneal thickness (CCT) would be approximately 500 μm [4–7], meaning that excessively thin or thick corneas would generate underestimations or overestimations of the IOP, respectively [4, 7, 8]. With the advent of more sophisticated devices capable of measuring CCT, it became clear that it is much more variable than Goldmann predicted [5–7]. More recently, some studies like the Ocular Hypertension Treatment Study (OHTS) stated CCT as an important confounder of Goldmann applanation tonometer (GAT) measurements [5, 6, 8]. Beyond this, factors like astigmatism, the examiner's competence, direction of gaze, tear thickness, corneal hydration, connective tissue composition, bioelasticity, corneal curvature and other corneal biomechanical properties are also important sources of error in GAT [2–4, 8]. Currently, there is not yet an accepted formula to correct IOP [4, 6, 7].

The Ocular Response Analyzer (ORA) was introduced in 2005, classified as a non-contact tonometer [2, 3, 5, 9]. This tonometer allows the measurement and evaluation of corneal biomechanical properties, namely the corneal hysteresis (CH), corneal resistance factor (CRF), corneal compensated intraocular pressure (IOP_{cc}) [3, 5] and also CCT and Goldmann correlated intraocular pressure (IOP_g) [3, 5]. Briefly, the ORA produces a rapid air pulse that deforms the cornea curvature [2, 3, 5, 9] and records the corneal deformation [2, 9]. When the cornea is moving inwards, it reaches a first applanation state (P1) [2, 3, 9]. After a slightly concave state [2, 3, 9], the air pulse pressure decreases and the cornea moves outwardly, passing through a second applanation state (P2) [2, 3, 9]. The average of P1 and P2 is IOP_g - analogous to the IOP

measured by GAT [2, 5, 9] - being the difference between these two values the value of CH [2, 3, 5].

The OHTS revealed that CCT is an important and independent risk factor for the development of glaucoma [4–6, 10]. These results were validated in the European Glaucoma Prevention Study (EGPS) [4, 5]. In fact, it was found a two-fold increased risk for the progression to glaucoma over 5 years for each 40 μ m thinning of the central cornea [4], meaning that a patient with a thinner cornea has more risk of glaucoma progression [4, 6]. However, this was not true in other studies. For instance, in the Early Manifest Glaucoma Trial (EMGT), with 5 years of follow up, CCT was not a significant predictive factor for glaucoma progression [4]. The value of CCT as significant predictive factor for the progression of glaucoma was only true for those patients with higher baseline IOP and not for those with lower baseline IOP after 11 years of follow up [4]. Furthermore, other studies, such as the Barbados Eye Study, the ones by Chauhan et al and Congdon et al, did not find any association between CCT and glaucoma [2, 4].

Interestingly, Nathan Congdon and colleagues showed that CH is associated with glaucoma progression risk [2, 5, 9]. This evidence suggests that low CH is associated with glaucomatous visual field damage and optic nerve defects [2, 9]. In fact, CH may be more strongly associated with glaucoma diagnosis, risk of progression and effectiveness of glaucoma treatments than CCT itself [2, 9].

All in all, the biological link between the biomechanical properties of the eye and glaucoma development and progression [4–6] remains to be understood.

Our review aimed to investigate the association between CH and CCT with glaucoma development.

METHODS

Our study is the first review of the literature and meta-analysis collecting CCT and CH data from adults with glaucoma and healthy controls in order to discuss differences in those two outcomes for both groups. This study started on July 2016.

Eligibility criteria

In this study, we only considered observational studies including adult patients (with a diagnosis of open angle glaucoma) and a control group reporting CCT and CH as outcomes.

Other studies with any other ophthalmologic diagnosis that could affect IOP, studies not written in English, with an interventional design, with a non-healthy control group, paediatric patients and volunteers (age < 18 years) and which did not provide outcome values for each group separately, were excluded.

We used this selective criteria to obtain a homogenous glaucoma and glaucoma related population with a healthy control group. We excluded any other diagnosis as a cause of the IOP and all interventional studies in order to reduce the possible bias associated with a heterogeneous group of diagnosis and the possible bias of procedures and medications performed during the studies.

Information sources and Search

MEDLINE was used as an information source and the search terms used were “hysteresis”, “glaucoma” and “corneal thickness”, from 2006 throughout July-2016. Since CH and CCT were our primary outcomes, we used “glaucoma”, “hysteresis” and “corneal thickness” as search terms in order to get access to a non-restrictive group of studies on this topic for further consideration.

Study selection:

A total of 124 articles were found with this search criteria. The abstract from each article was used for screening, one of them was found to be duplicated. After screening, we found $n = 45$ studies, from which 2 were written in French, 2 written in German, 1 was written in Czech, 3 included paediatric populations, 1 had no outcome information, 2 studies had a case group including more than just glaucoma diagnosis, 2 provided the data from control and case groups together, 6 had a non-healthy control group and 7 were interventional studies.

For comparative and quantitative purposes, 19 studies, from 2008 throughout 2016, were considered for analysis. This information is presented in Figure 1, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

Data collection process and statistical analysis

The selected full texts were collected and assessed for demographic data and reported outcomes. For the statistical analysis, we used the mean difference (MD) between groups (patient - control) of CH and CCT, respectively.

RESULTS

From a total of 124 studies screened, only 19 of them complied with our eligibility criteria, as shown in Figure 1. Table 1 and Figures 2-3 summarize the mean and standard deviation (SD) of both CH and CCT for the control and case groups of each study.

Synthesis of results

A total of 1213 glaucoma eyes, arising from 1159 glaucoma patients and 1055 healthy eyes from 1021 healthy subjects, were considered in our study. Table 1 shows the baseline characteristics of these participants and their eye-related parameters.

A quantitative analysis showed us that CH was significantly lower in the glaucoma group when compared to the control group (MD = $-1.54\ \mu\text{m}$, 95% CI $[-1.68, -1.41]$, $P < 0.00001$) as shown in Figure 2. As we can observe in Figure 3, CCT was also significantly lower in the glaucoma group when compared to healthy controls (MD = $-8.49\ \mu\text{m}$, 95% CI $[-11.36, -5.62]$, $P < 0.001$).

DISCUSSION

Summary of evidence, limitations and conclusions

The latest evidence is still unclear regarding the true value of CCT as a risk factor for glaucoma. While some studies stand up for CCT as an important risk factor for the development of glaucoma [4–6, 10], others like EMGT, Barbados Eye Study, Chauhan and Congdon, did not find such a simple and linear relationship between those two parameters [2, 4]. According to our study, there is a significantly lower CCT value among glaucoma patients (mean difference 8.49 μm , range [-11.36, -5.62], 95% CI; $P = 0.0005$) compared to the control group. However, it is hard to draw simple conclusions about the meaning of this difference for the two groups, since it is different to applanate a thinner or a thicker surface, becoming easier or harder to applanate the cornea, respectively [9]. So, in other words, CCT may result in a confounding factor for IOP measured by GAT rather than an independent risk factor for the disease.

The ORA device give us several biomechanical properties that are assumed to be less influenced by CCT when compared to GAT, namely CH, which is a biomechanical property related to the viscoelasticity of the cornea. According to our results, there is a significantly lower CH among glaucoma patients, compared to healthy controls (mean difference 1.54 mmHg, range [-1.68, -1.41], 95% CI; $P < 0.00001$), which is in agreement with previous results from other studies [2, 9]. Since ORA is a non-contact tonometer [2, 3, 5, 9], parameters measured by this device may be more reliable than GAT [2, 3].

From these study results, a relevant question that rises is about the applicability of CH as an instrument in clinical practice and its reliability. Standard CCT measurements have been widely used and may help interpret IOP findings, but up to this day it remains undetermined whether this variable per se is useful for assessing a patient's risk factor on developing the disease. In this sense, by providing further information about the corneal biomechanics, CH may be different. However, there is still not a consolidated evidence that allow us to replace the use of CCT for other marker such as CH, in the management of glaucoma patients. The fact that CH is not theoretically influenced by CCT [3, 5, 8, 9], which shows a large variability in the overall population [5–7], is very important, so it can become a valuable tool, for example, on the assessment of the stratification risk for glaucoma patients or even for prognosis. Yet, ORA is an instrument that is not commonly found in ophthalmology clinics worldwide, which limits the knowledge of CH in glaucoma.

The results of our study show a strong evidence on the subject. Furthermore, it should be pointed out that this is the first study review of the literature and meta-analysis about this topic involving corneal hysteresis in glaucoma. However, we recognize that our study has some limitations. We highlighted the fact that we include several glaucoma diagnosis [POAG, normal tension glaucoma (NTG), pre-perimetric POAG, pseudoexfoliative glaucoma (PEXG) and exfoliative glaucoma (EXG)], which can also bias the results, once the different physiopathology of each type of glaucoma may have a different impact on the cornea. Additionally, our study only considered articles from 2008 through 2016, based on a strict criteria. Furthermore, the ORA device was only introduced in 2005. So, these two factors resulted in a relatively short period under review in our study. Finally, we also recognise some other limitations, namely, the fact that it is not a systematic review, that it has not a risk of bias evaluation and that we have only included observational studies with the purpose to eliminate the risk of bias from interventions in the groups.

Concluding, our study reveals a significant difference on CH and CCT between glaucoma patients and healthy controls. These results show that maybe the true assessment is beyond CCT measurement alone. So, it is important to keep searching for new and more sophisticated tools to measure corneal properties, as CH, to deepen our knowledge in this subject.

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FIGURES

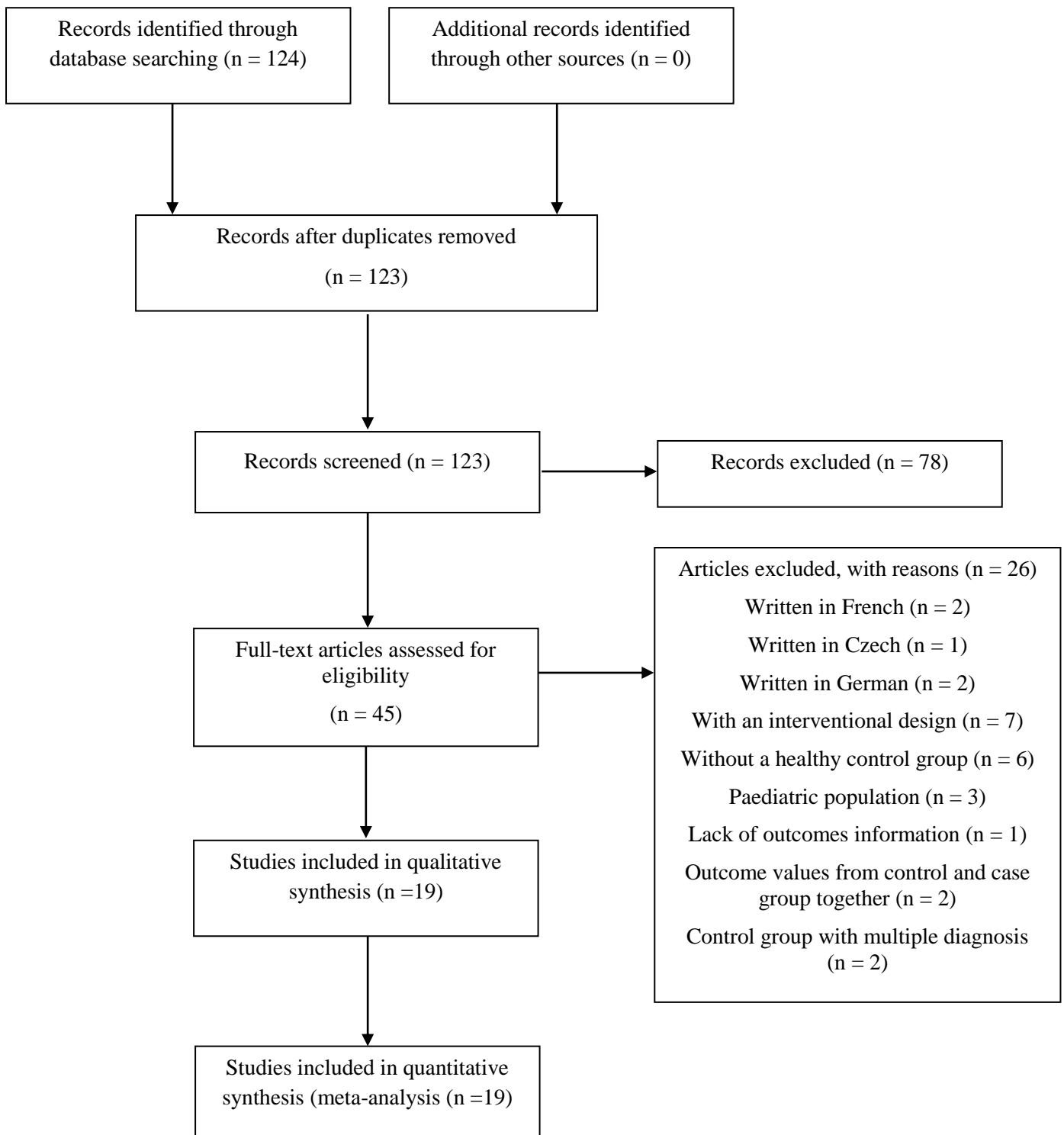


Figure 1: Study flow-diagram

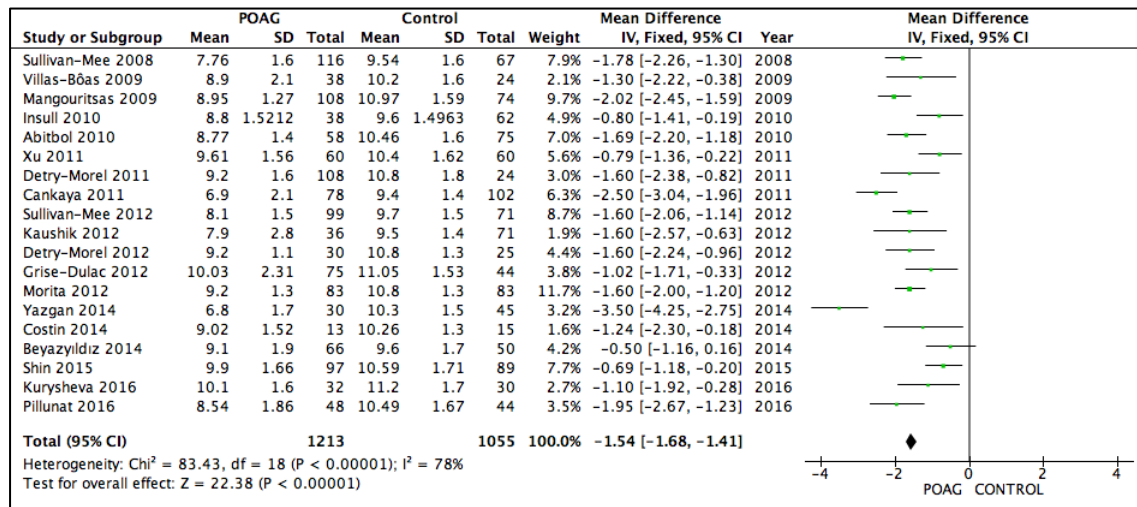


Figure 2: Corneal Hysteresis - Forest plot
CI = confidence interval. SD = Standard deviation.

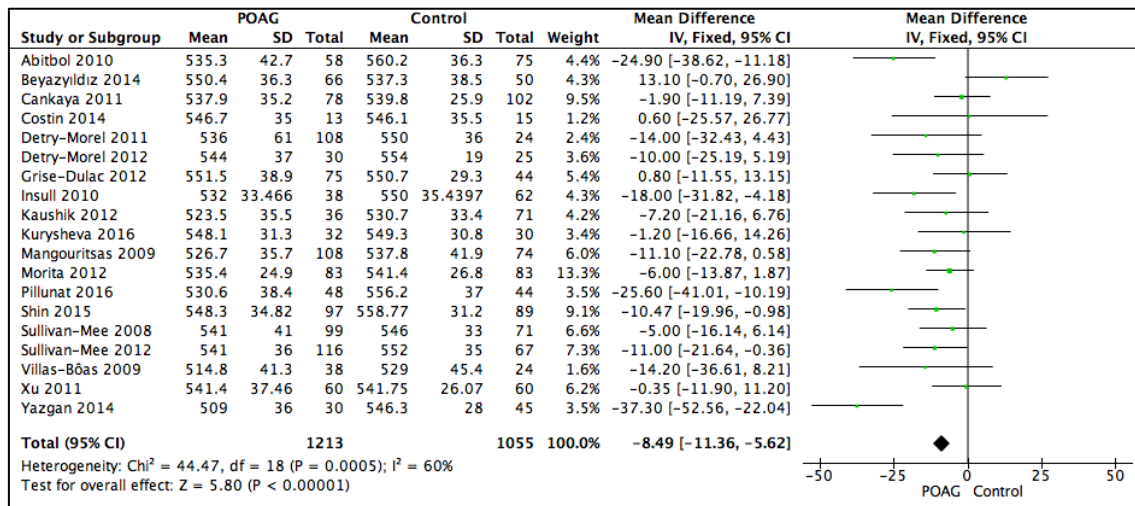


Figure 3: Central Corneal Thickness - Forest plot
CI = confidence interval. SD = Standard deviation.

TABLES

Table 1: Baseline characteristics

Article	Diagnosis	No. of patients	No. of eyes	CH	CCT
				Mean \pm SD (mmHg)	Mean \pm SD (μ m)
Kuryшева, 2016	Glaucoma	32	32	10,1 \pm 1,6	548,1 \pm 31,3
	Control	30	30	11,2 \pm 1,7	549,3 \pm 30,8
Pillunat, 2016	Glaucoma	48	48	8,54 \pm 1,86	530,6 \pm 38,4
	Control	44	44	10,49 \pm 1,67	556,2 \pm 37
SHIN, 2015	Glaucoma	97	97	9,9 \pm 1,66	548,3 \pm 34,82
	Control	89	89	10,59 \pm 1,71	558,77 \pm 31,19
Beyazyıldız, 2014	Glaucoma	66	66	9,1 \pm 1,9	550,4 \pm 36,3
	Control	50	50	9,6 \pm 1,7	537,3 \pm 38,5
Yazgan, 2014	Glaucoma	30	30	6,8 \pm 1,7	509 \pm 36
	Control	45	45	10,3 \pm 1,5	546,3 \pm 28
Costin, 2014	Glaucoma	13	13	9,02 \pm 1,52	546,7 \pm 35
	Control	15	15	10,26 \pm 1,3	546,1 \pm 35,5
Insull, 2010	Glaucoma	38	38	8,8 \pm 1,5212	532 \pm 33,466
	Control	62	62	9,6 \pm 1,4963	550 \pm 35,4397
Sullivan-Mee, 2012	Glaucoma	116	116	7,76 \pm 1,6	541 \pm 36
	Control	67	67	9,54 \pm 1,6	552 \pm 35
Kaushik, 2012	Glaucoma	36	36	7,9 \pm 2,8	523,5 \pm 35,5
	Control	71	71	9,5 \pm 1,4	530,7 \pm 33,4
Detry-Morel, 2012	Glaucoma	30	30	9,2 \pm 1,1	544 \pm 37
	Control	25	25	10,8 \pm 1,6	554 \pm 19
Morita, 2012	Glaucoma	83	83	9,2 \pm 1,3	535,4 \pm 24,9
	Control	83	83	10,8 \pm 1,3	541,4 \pm 26,8
Cankaya, 2011	Glaucoma	78	78	6,9 \pm 2,1	537,9 \pm 35,2
	Control	102	102	9,4 \pm 1,4	539,8 \pm 25,9
Grise-Dulac, 2012	Glaucoma	38	75	10,03 \pm 2,31	551,5 \pm 38,9
	Control	22	44	11,05 \pm 1,53	550,7 \pm 29,3
Detry-Morel, 2011	Glaucoma	108	108	9,2 \pm 1,6	536 \pm 61
	Control	24	24	10,8 \pm 1,8	550 \pm 36
Xu, 2011	Glaucoma	60	60	9,61 \pm 1,56	541,4 \pm 37,46
	Control	60	60	10,4 \pm 1,62	541,75 \pm 26,07
Abitbol, 2010	Glaucoma	58	58	8,77 \pm 1,4	535,34 \pm 42,7
	Control	75	75	10,46 \pm 1,6	560,2 \pm 36,3
Villas-Bôas, 2009	Glaucoma	21	38	8,90 \pm 2,1	514.80 \pm 41.3
	Control	12	24	10.20 \pm 1.6	529.00 \pm 45.4
Mangouritsas, 2009	Glaucoma	108	108	8,95 \pm 1,27	526,77 \pm 35,73
	Control	74	74	10,97 \pm 1,59	537,84 \pm 41,93
Sullivan-Mee, 2008	Glaucoma	99	99	8,1 \pm 1,5	541 \pm 41
	Control	71	71	9,7 \pm 1,5	546 \pm 33

CCT = central corneal thickness. CH = corneal hysteresis. No = number.
SD = standard deviation